



Local ablative therapy in oncogenic-driven oligometastatic non-small cell lung cancer: present and ongoing strategies – a narrative review

Vincent Fallet¹, Lise Matton¹, Antoine Schernberg², Anthony Canellas¹, François H. Cornelis^{3^}, Jacques Cadranel¹

¹Department of Pneumology and Thoracic Oncology, Assistance Publique-Hôpitaux de Paris, Hôpital Tenon and GRC 4, Therascan, Sorbonne Université, Paris, France; ²Department of Radiation Oncology, DMU Orphé, Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Sorbonne Université, Paris, France; ³Department of Interventional Radiology and Oncology, Assistance Publique-Hôpitaux de Paris, Hôpital Tenon, Sorbonne Université, Paris, France

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Correspondence to: Jacques Cadranel, Department of Pneumology and Thoracic Oncology, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, 4 rue de la Chine, 75970 Paris, France. Email: jacques.cadranel@aphp.fr.

Abstract: Oligometastatic (OM) disease is defined by a low metastatic tumor spread. OM non-small cell lung cancer (NSCLC) treatment aims to improve the patient's prognosis and quality of life, in an attempt-to-cure objective. Oncogenic-driven metastatic NSCLC accounts for about 20–25% of NSCLCs, with an ever-increasing number of potentially druggable molecular alterations. Due to specific targeted therapy, the care and prognosis of mutated NSCLC is quite different from non-oncogenic-driven NSCLC. However, OM-NSCLC treatment guidelines do not specifically discuss oncogenic-driven OM-NSCLC patients. We conducted a narrative review regarding retrospective and prospective studies published from inception to May 2020 dealing with oncogenic-driven OM-NSCLC in order to: (I) describe the specific patterns of metastatic spread of oncogenic-driven NSCLC (i.e., bone and pleural tropism in EGFR mutated NSCLC and serous and brain metastases in ALK NSCLC); (II) review the low level of current evidence for local ablative therapy (LAT) strategies in patients with oncogenic-driven OM-NSCLC, focusing on the benefit/risk of tyrosine kinase inhibitors (TKI) and LATs combination and (III) present strategies to help to select the best candidate for an attempt-to-cure approach. Finally, the optimal strategy may be to introduce a targeted therapy, then treat all tumor sites with LAT, and finally continue TKI for unknown prolonged duration in an attempt to prolong progression free survival in most patients, improve overall survival for some patients, and potentially lead to a cancer cure for a few patients.

Keywords: Non-small cell lung cancer (NSCLC); oligometastatic; epidermal growth factor receptor (EGFR); anaplastic lymphoma kinase (ALK)

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[^] ORCID: Vincent Fallet, 0000-0002-5153-6951; François H. Cornelis, 0000-0002-1058-0884.

Introduction

The oligometastatic (OM) stage is a rare and intermediate stage of cancer that reflects a moderate risk of the disease's metastatic spread. Treating OM non-small-cell lung cancer (NSCLC) aims to improve the patient's prognosis and quality of life by implementing long-term disease control. Thanks to advances in interventional radiology and radiotherapy, the combination of systemic therapy with local ablative therapy (LAT) improves survival. Finally, systemic treatment may be interrupted through an "attempt" rather in an "intent"-to-cure approach, although currently there is no evidence to achieve this goal in the setting of oncogenic addictions.

Recently, the European Society of Medical Oncology (ESMO) introduced guidelines for treating synchronous OM-NSCLC (1,2). These recommendations are "general" and do not consider specific NSCLC subgroups, such as oncogenic-driven lung cancer, and long-term tumor responses to immunotherapy.

In recent years, the prognosis of oncogenic-driven metastatic NSCLC has continuously improved, owing to widespread molecular tumor assessment when lung cancer is diagnosed, and the use of the latest-generation targeted therapy. Oncogenic-driven metastatic NSCLC accounts for about 20–25% of NSCLCs, with an ever-increasing number of potentially druggable molecular alterations. It usually occurs in non-smokers or light-former smokers, females and persons from Asian countries presenting with metastatic primary lung adenocarcinoma. Actually, the most common therapeutic alterations are the *epidermal growth factor receptor (EGFR)* mutation (10–30%), *anaplastic lymphoma kinase (ALK)* rearrangements (4–6%), *c-ROS oncogene 1 (ROS1)* rearrangements (2–3%), *B-Raf proto-oncogene serine/threonine kinase (BRAF)* mutations (2–4%), *rearranged during transfection (RET)* gene rearrangements (1–2%), *human epidermal growth factor receptor 2 (HER2)* mutation and amplification (1–2%), *mesenchymal-to-epithelial transition gene (MET)* exon 14 alteration and amplification (3–4%), and recently, *neurotrophic tropomyosin receptor kinase (NTRK)* mutations (1–2%) (3-5).

Osimertinib, a third-generation tyrosine kinase inhibitor (TKI), has demonstrated superiority in metastatic-naïve EGFR-mutated NSCLC, compared to first-generation TKIs, with median overall survival (OS) of 38.6 months versus 31.8 months, respectively [hazard ratio (HR) for death: 0.80; P=0.046] (6). In metastatic naïve ALK-positive NSCLC, alectinib and brigatinib prolong progression free

survival (PFS), compared to crizotinib, but OS data are still immature (7,8).

Despite the significant activity of these new-generation TKIs, these treatments remain palliative, but they enable the prolonged control of the cancer and improve quality of life through significant improvement in OS. However, tumors are molecularly heterogeneous and invariably develop a mechanism of resistance under pressure from a TKI and subsequently progress (9). Several strategies are being evaluated to maximize the prognosis of advanced NSCLC with oncogenic addiction, such as the continuation of treatment beyond progression, which is associated with LAT (2), and more recently, first-line drug combinations to delay molecular resistance and improve OS (10-13). Although these strategies improve the prognosis of metastatic oncogenic-driven NSCLCs, they have not yet achieved the curative goal, as opposed to cancer that is controlled by immunotherapy, in which a plateau in the OS curves has been observed. As previously seen, the care and prognosis of mutated NSCLC is quite different from non-oncogenic-driven NSCLC. In our opinion, the management of oncogenic-driven OM-NSCLC also requires specific recommendations.

This review aims to present and discuss the strategy of care for oncogenic-driven OM-NSCLCs that are treated using a LAT. Utilization of a LAT is only possible when the disease has not extended, so we will first define different OM diseases using a care-taking lens. The features of NSCLC with addiction will then be described to guide different strategies in this specific population. Next, an analysis of the literature will discuss strategies, particularly with regards to treating OM-NSCLC with addiction. Finally, the paper presents the specifics of LAT that are associated with targeted therapies.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-1152>).

Literature review

A systematic Medline search using PubMed, the Cochrane database, and Google Scholar was performed from inception to May 2020. All retrospective and prospective studies, systematic reviews, and meta-analysis series in English dealing with oncogenic-driven OM-NSCLC were included. Case reports, editorials, studies with fewer than 10 patients, studies without LAT were excluded. Bibliographies from selected articles were screened for relevant publications.

However, data extracted from meeting abstracts were only minimally used. Finally, 32 publications were deemed to be relevant to the topic of OM-NSCLC with addiction and are the subject of this systematic review. All articles were reviewed by at least two authors (JC, VF, LM, and AS).

Should we change the definition of OM disease in oncogenic-driven NSCLC?

No specific definition has been proposed for OM disease in oncogenic-driven NSCLC. Currently, it is widely accepted that this is defined by the presence of ≤ 5 metastases and the involvement of three organs, which reflects a moderate risk of metastatic disease spread. All metastases should be treated using LAT (14,15). However, in our opinion, metastatic sites are not all equal. For example, pulmonary lymphangitis, pleural/serous effusion, and meningitis are not accessible to LAT. Mediastinal node involvement is an essential adverse prognostic factor for OS in patients with OM-NSCLC (16).

OM disease also represents an umbrella term for a dynamic state model of disease spreading (17). Synchronous metastases are detected within ≤ 6 months of the initial cancer diagnosis; if they are detected later, they are considered metachronous. Guckenberger *et al.* performed a subclassification into oligo-recurrence, oligo-progression, and oligo-persistence, while taking into account whether OM disease is diagnosed during a treatment-free interval or during the first line of active systemic therapy, and whether an OM lesion has progressed on current imaging or not (*Figure 1*).

In our opinion, fluorodeoxyglucose F 18 positron emission tomography (^{18}F FDG-PET) and brain magnetic resonance imaging (MRI) imaging should be considered mandatory, especially in the context of oncogenic-driven cancers. Brain MRI is significantly superior to brain computed tomography (CT) in terms of detecting brain metastases, as the former detects lesions that are not visible on CT, especially for ALK-rearranged lung cancer (see below). The quality of the initial staging assessment of OM patients is essential (14,18). Unfortunately, most studies do not provide details of initial staging, or they were conducted prior to the widespread use of modern imaging techniques (19,20).

Are metastatic sites different in oncogenic-driven OM-NSCLC than in other cancers?

It is particularly complicated to define patterns of OM-

NSCLC with oncogenic addiction, because the data about this population are poor. Since some mutations are extremely rare, there are no available studies concerning every currently known oncogene alteration. There is also heterogeneity within cohorts of the same oncogene driver alteration, with different mutations and different associated prognoses, such as in EGFR mutations between the L858R and del19 subgroups. In their meta-analysis, which included 21 studies, Giaj-Levra *et al.* collected data from six studies focused on OM-NSCLC with oncogenic addiction, corresponding to only 5.6% of the total analyzed population. This only concerned patients with EGFR mutations or ALK gene rearrangements (21). The mean number of metastatic disease sites seemed to be significantly higher in the ALK-positive cohort than in the triple-negative cohort, with 3.6 sites in one study that investigated 209 patients, including 41 with ALK-positive NSCLC (22). The number of lesions per metastatic site from these studies is often unknown. It is also unclear whether ^{18}F FDG-PET is widely used to determine the initial metastatic status, the proportion of patients with brain imaging is low or unknown in these studies, and the technique used on those who benefited is often not specified.

At diagnosis, EGFR-mutated NSCLC (*Figure 2*) is likely to be significantly associated with metastatic bone and pleural disease, and possibly with liver disease, too (22-25). Results are contradictory concerning the association between brain metastases and EGFR-mutated status (23,24,26-28). ALK-positive NSCLC (*Figure 2*) is associated with a metastatic serous tropism, with higher incidence of pericardial and pleural metastases, extra-thoracic nodes, liver metastases brain and lung metastases compared with non-, EGFR-, or KRAS-mutated patients (22,23,24). In the KRAS-mutated population (*Figure 2*), there are more pulmonary metastases (24).

In the case of recurrent disease after surgery, we found the same trend with pleural and pericardial spreads in the ALK group, as well as with liver spreads in the ALK- and EGFR-mutated groups (22). It seems that patients with an EGFR mutation have more often disease progression in the brain after surgery and less often adrenal gland metastases, compared to non-mutated patients (29). Disease free-survival after surgery appears to be significantly longer for EGFR-mutated patients. The subtype of the EGFR mutation could influence the recurrence pattern, with a lower risk of distant-spread disease and better local control, in patients exhibiting exon19 Del (29).

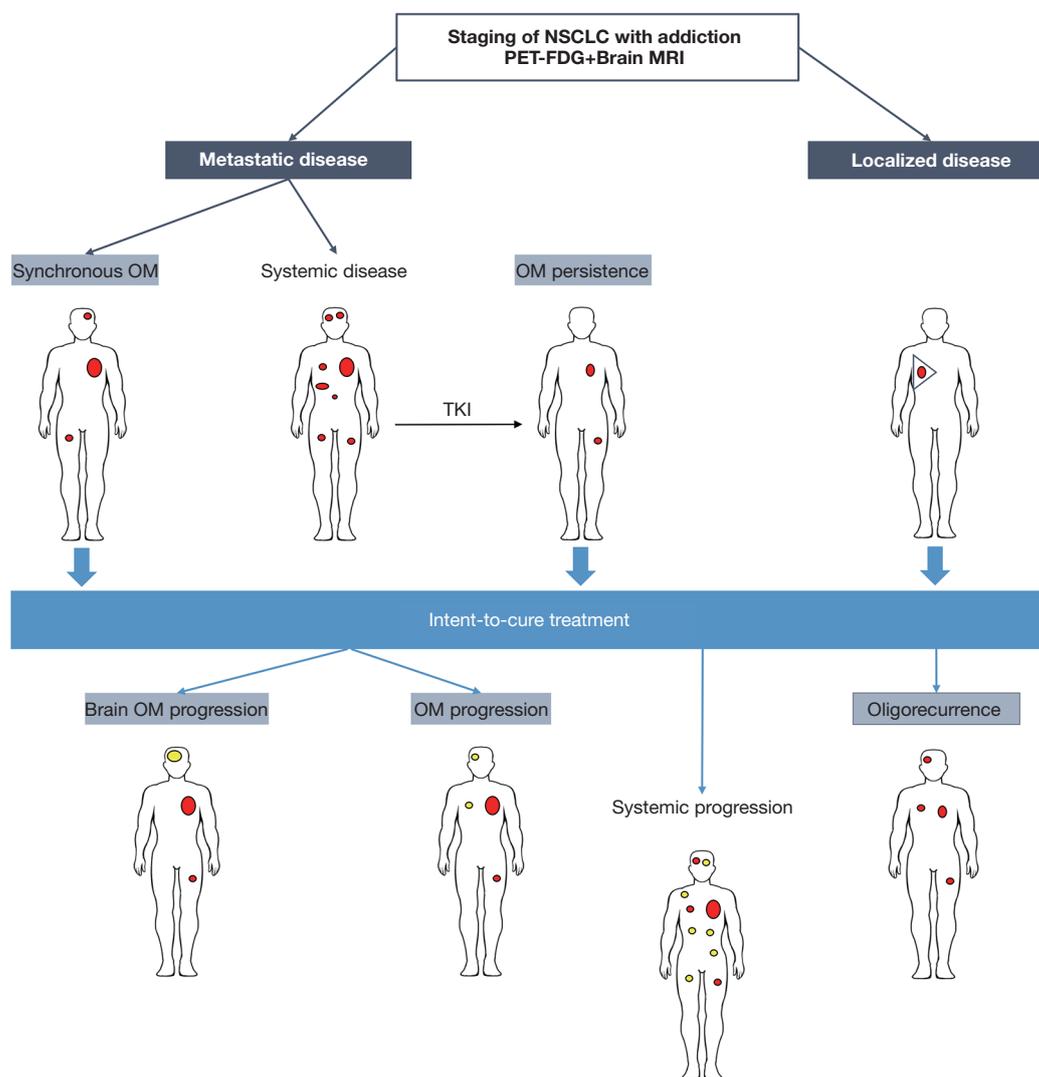


Figure 1 Schematic of different definitions of OM disease.

Is the prognosis for OM oncogenic-driven NSCLC different than that for cancers without addiction?

Large trials concerning the treatment of OM-NSCLC have only included a small number of patients exhibiting cancers with addiction, mainly those with an *EGFR* mutation or *ALK* rearrangement (19,20,30-33). The presence of oncogenic addiction was a good prognostic factor for OS. In a Phase 2 trial of OM-NSCLC, 49 patients with less than four metastases after first-line treatment were randomized to receive either LAT or standard treatment (maintenance or monitoring). LAT was radiotherapy (hypo-fractionated or stereotaxic) and/or surgery. After a median follow-up of

38.8 months, median updated OS was 41.2 months in the LAT arm (18.9 months–not reached) versus 17.0 months in the maintenance arm (10.1–39.8 months; $P=0.017$) (20,30). This trial included five patients with addiction: three with an *EGFR* mutation and two with an *ALK* rearrangement. The median OS was not reached in this group. Despite this small number of patients with addiction, multivariate analysis demonstrated that the presence of *ALK/EGFR* alterations and a small number of metastases were associated with better OS in the LAT treatment arm (HR: 0.46; 0.21–0.99; $P=0.048$).

Parikh *et al.* prospectively analyzed 186 patients with OM-NSCLC, which was defined as ≤ 5 metastases. Overall, 20 patients (12%) exhibited *EGFR* mutations and four (20%)

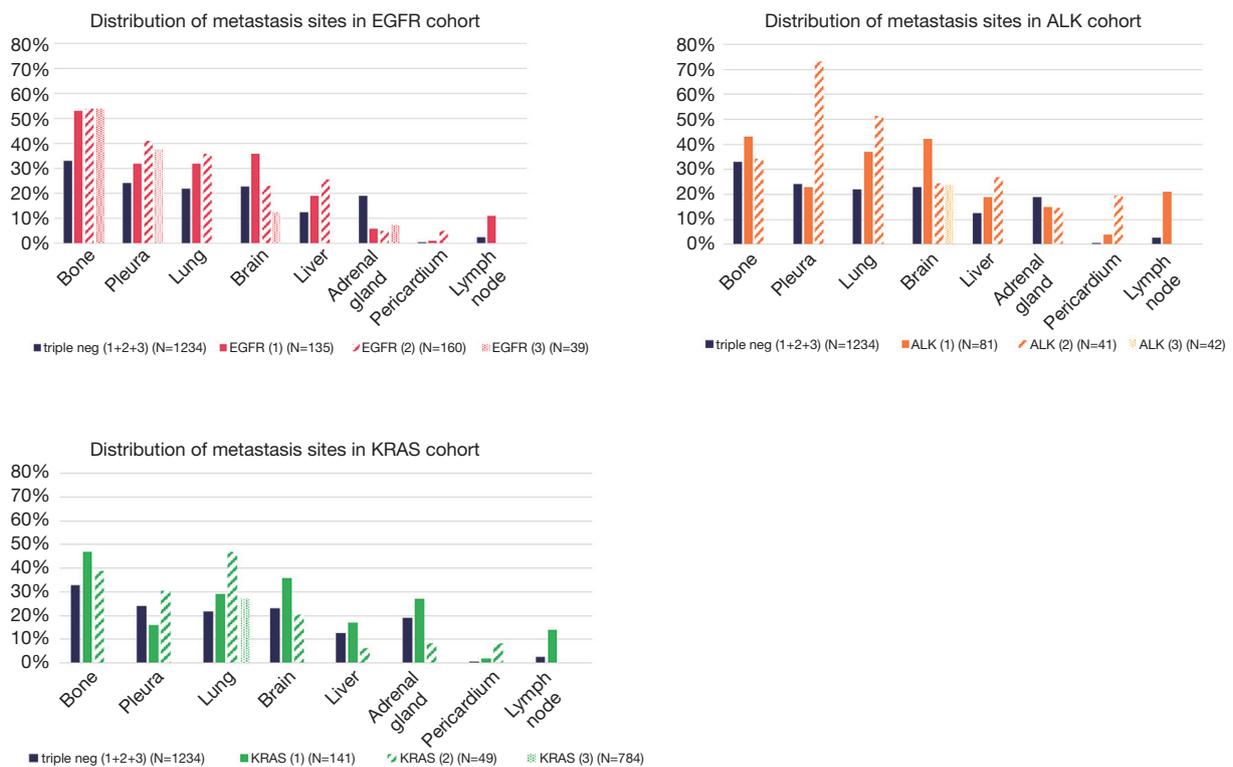


Figure 2 Distribution of metastasis sites according to mutation status in patients with Stage IV non-squamous NSCLC. Frequency of metastasis spread in (I) Dormieux *et al.* (23); (II) Doebele *et al.* (22); and (III) Kuijpers *et al.* (24).

received LAT for a primary tumor. Achieving LAT does not appear to have been influenced by EGFR status. LAT on the primary tumor and EGFR mutation were associated with prolonged OS (HR: 0.65; P=0.043 and HR: 0.46; P=0.001, respectively). Poor prognosis factors were PS2 (HR: 2.43; P=0.02), N2N3 lymph node status (HR: 2.16; P<0.001), epidermoid subtype (HR: 1.97; P=0.001) and the presence of metastasis in several organs (HR: 2.11; P=0.001) (31).

Finally, no trials reported over-toxicity when comparing patients that received the combination of LAT and targeted therapy, with those who received chemotherapy (19,20,30-35). As in the multi-metastatic stage, the presence of an EGFR or ALK addiction seems to be a factor of good prognosis in OM disease. However, it is difficult to identify whether such better prognosis is directly related to the presence of addiction, associated factors (i.e., ethnicity, gender, or non-smoker status), or the major and prolonged effect of targeted therapy.

Therapeutic strategies for OM oncogenic-driven NSCLC

Two first-line strategies have been described in the

literature. OM disease is either defined at the initial assessment, which is known as “synchronous” OM, or in response to systemic treatment, which is referred to as “oligo-persistent” status. LAT may also differ according to the intention-to-treat strategy, which can vary between lesions from all sites, only lesions at the primary site, or lesions at all the metastatic sites being treated. The main studies combining LAT and targeted therapy in the first-line setting are summarized in *Tables 1-3*, according to the intention-to-treat LAT strategy. To date, all studies evaluating strategies for OM with addiction concern EGFR-mutated NSCLC.

Therapeutic strategies for synchronous EGFR-mutated OM-NSCLC

LAT of at least one tumor site is associated with better prognosis

Hu *et al.* analyzed 231 EGFR-positive OM-NSCLCs (one organ and <6 metastases) in a retrospective cohort. All patients received a first-generation EGFR-TKI. LAT was administered

Table 1 Selected studies of local ablative therapy for metastases in EGFR oligometastatic non-small-cell lung cancer: characteristics and clinical outcomes

Study	Number of patient n (LAT)/n (control)	Study type	OM type	OM definition and organ involved	Mandated ¹⁸ FDG PET/ brain MRI	Type of LAT	Addiction and systemic therapy concomitantly	PFS (median)	OS (median)
Hu, Xu, et al. 2019	143/88	Retrospective single-center	Oligometastatic synchronous (n=96) and oligorecurrent (n=135)	<1 organ and <6 metastases; bone (37%), brain (34%), lung (22%)	No/No	Only metastases; radiotherapy or surgery	TKI EGFR 1 st Ge	15 vs. 10 months (P=0.000)	34 vs. 21 months (P=0.001)
Hu, Li, et al. 2019	62/65	Retrospective single-center	Oligometastatic synchronous (n=79) and oligorecurrent (n=48)	<6 metastases only bone	No/No	Bone metastases; radiotherapy 91.9%; both surgery (4.8%); both (2.2%)	TKI EGFR 1 st Ge	14.0 vs. 8.1 months (P=0.01)	36.3 vs. 21.0 months (P=0.01)
Jiang et al. 2019	47/45	Retrospective single-center	Oligometastatic synchronous (n=64) and oligoprogressive (n=71)	<5 metastasis only liver	No/No	Liver metastases; radiotherapy, RFA, interventional therapy, or surgery	TKI EGFR 1 st Ge	13.8 vs. 8.6 months (P=0.001)	31.2 vs. 18.5 months, (P=0.001)

RFA, radiofrequency ablation; TKI EGFR 1st Generation: erlotinib icotinib or gefitinib; OM, oligometastatic; LAT, local ablative therapy; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor.

to 143 (61.9%) patients (all radiotherapy modalities or surgery). No treatment of T and N was delivered in this study. Oligo-progressive patients who had undergone initial surgery and relapsed in the OM stage were included (n=135/231, 58.4%). Metastatic sites were bone (n=87), brain (n=80), and lung (n=51). The LAT group exhibited more brain metastases. Median PFS and OS were significantly increased in the LAT group, with median PFS of 15 months versus 10 months (HR: 0.610; P<0.001) and median OS of 34 months versus 21 months (HR: 0.593; P=0.001) (25). No difference was found according to the EGFR mutation type (del19 or L858R). The OS benefit of LAT was also found for the same group in EGFR NSCLCs, with only bone or hepatic metastases. Analysis revealed a median OS of 36.3 versus 21.0 months (HR: 0.537; P=0.01) and median PFS of 31.2 versus 18.5 months (P=0.001) (36,37).

Elamin *et al.* compared the outcomes of 12 patients with EGFR-mutated OM-NSCLC who were treated with a combination of an EGFR-TKI consolidative LAT with 129 patients were treated with only an EGFR-TKI (38). Positive thoracic nodes counted as one lesion. In the consolidative LAT group, eight patients (66.7%) had less than four metastases. LAT consisted of hypo-fractioned radiotherapy (n=11) or lung surgery (n=1), either on the primary site or metastases. Median PFS significantly improved in the LAT group (36 vs. 14 months; P=0.0024), but median OS was not significantly different. No significantly increased toxicity was observed (38).

Combined with EGFR- or ALK-TKI, a study by Borghetti *et al.* found that stereotaxic radiotherapy (SRT) to at least one tumor site was a better factor of OS than palliative radiotherapy (RT). Nearly half of patients (n=52, 49.1%) were defined as OM or oligo-progressive, with less than five metastases. OS was 79% at one year and 62% at two years in this subgroup (39).

Recently, a Chinese randomized multicenter Phase 2 trial evaluated concomitant SBRT and EGFR-TKI, versus EGFR-TKI alone, for EGFR OM-NSCLC (up to three metastatic sites). The results were presented at the 2019 World Conference for Lung Cancer (WCLC) (40). After three months of TKI with controlled disease, 61 patients were randomized to either SBRT combined with TKI or TKI alone. Investigators decided which sites would be irradiated (primary tumor, metastasis, or both). Median follow-up was 22.3 months. Median PFS of patients with SBRT combined with TKI (n=30) was superior to that for those on TKI alone (n=31; 17.4 vs. 8.9 months; P=0.042). In multivariable analysis, PFS varied according to the

Table 2 Selected studies of local ablative therapy for primary and/or metastases in EGFR oligometastatic non-small cell lung cancer: characteristics and clinical outcomes

Study	Number of patient n (LAT)/n (control)	Study type	OM type	OM definition and organ involved	Mandated ¹⁸ F-DG PET/ brain MRI	Type of LAT	Addition and systemic therapy concomitant	PFS (median)	OS (median)
Peng et al. 2019	30/31	Phase 2 Multicenter	Oligometastatic synchronous (no progression after 3 months TKI)	<4 metastasis	Unknown	Primary and/or metastases SBRT	EGFR (common) TKI EGFR 1 st Ge (interim)	17.4 vs. 8.9 months (P=0.042)	No mature OS
Ni et al. 2020	34/52	Retrospective Single-center	Oligometastatic (no progression after 3 months TKI)	Extracranial <6 metastasis lung (39.5%), liver (23.3%), bone (14%), adrenal gland (16.2%), chest wall (7%)	No/No	Primary and/or metastases Microwave ablation	EGFR (common and uncommon (n=1)) TKI EGFR 1 st Ge	16.7 vs. 12.9 months (P=0.02)	34.8 vs. 22.7 months (P=0.04)
Elamin et al. 2019	12/129	Retrospective Single-center*	Oligometastatic (no progression after 3 months TKI)	≤3 metastases (n=8), >3 (n=4) (positive thoracic nodes counted as 1 lesion)	No/No	Primary and/or metastases Hypofractionated radiotherapy or SRT (n=11)/Lung surgery (n=1)	EGFR (common and uncommon (n=1; L861Q)) TKI EGFR (no osimertinib)	36 vs. 14 months (P=0.0024)	Not reached vs. 36 months (P=0.06)
Xu et al. 2018	106/39	Retrospective Single-center	Oligometastatic (no progression with TKI)	≤5 metastases (90% with ≤2 metastases)	No/No	Primary and/or metastases** Radiotherapy, surgery, radiofrequency	EGFR (common) TKI EGFR 1 st Ge	20.6 vs. 15.6 and 13.9 months (P<0.001)	40.9 vs. 34.1 and 30.8 months (P<0.001)

*, post hoc Phase 2 - Multicenter (n=3) + Database single-center (n=9); **, treatment group: n=51 with LAT in all site and n=55 with partial LAT. EGFR, epidermal growth factor receptor; LAT, local ablative therapy; OM, oligometastatic; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; EGFR common mutation: del 19 and L858R/uncommon: others; TKI EGFR 1st Generation: erlotinib icotinib or gefitinib; SRT, stereotaxic radiotherapy.

Table 3 Selected studies of local ablative therapy for primary and metastases in EGFR oligometastatic non-small cell lung cancer: characteristics and clinical outcomes

Study	Number of patient n (LAT)/ n (control)	Study type	OM type	OM definition and organ involved	Mandated ¹⁸ FDG PET/ cerebral MRI	Type of LAT	Addition and systemic therapy concomitantly	PFS (median)	OS (median)
Wang et al. Zeng 2020	68/65	Phase 3 Multicenter	Oligometastatic synchronous	Extracranial <6 metastasis (max 2/organ)	Yes/Yes	All sites, SRT	EGFR (common + ins20 TKI EGFR (no osimertinib)	20.20 vs. 12.5 months (P<0.001) (interim)	25.5 vs. 17.4 months (P<0.001) (interim)
Chan et al. 2020	16/NA (post hoc analysis with screen failure group n=43)	Phase 2 Multicenter	Oligoresidual after 3 months EGFR TKI	≤4 residual metastasis (lungs n=16, bones n=4 and lymph nodes n=2)	Yes/No	All sites, SRT	EGFR (common) TKI EGFR (no osimertinib)	15.2 months [vs. 11.1 months with screen failure group (P=0.043)]	44.3 months (no significant difference with screen failure group)

EGFR, epidermal growth factor receptor; LAT, local ablative therapy; OM, oligometastatic; PFS, progression-free survival; OS, overall survival; EGFR common mutation: del 19 and L858R; TKI, tyrosine kinase inhibitor; SRT, stereotactic radiotherapy.

irradiation field. PFS was longer in patients irradiated for just primary lesions, compared to those irradiated for both primary and metastatic lesions, or for those irradiated for metastatic lesions only (21.8, 18.3, and 10.6 months, respectively; P=0.006). OS data were not presented. The combined SBRT and TKI treatment was safe, and no patients experienced Grade 3 SBRT-related toxicities.

In all of these studies, which mostly employed a retrospective design, using LAT associated with TKI invariably improved prognosis, in terms of both PFS and OS. However, in these studies, not all tumor sites received LAT, so the goal cannot be curative. Some other studies evaluated this maximizing strategy.

LAT of all residual tumor sites in EGFR-mutated OM-NSCLC is associated with the best prognosis

The first study involving a retrospective cohort of EGFR-mutated OM-NSCLC who received LAT in all oligometastatic sites was performed in China (41). This study collected all cases of synchronous OM-NSCLC, which was defined as less than five metastases sites with a common EGFR mutation. All patients received a first-generation TKI (erlotinib, gefitinib, or icotinib) and were non-progressive at first evaluation. LAT was performed with curative intent, either by RT or surgery. Overall 145 patients were included: 51 received LAT at all tumor sites (including primary lesions [all site-LAT]), 55 received LAT either at the primary sites or on metastasis sites (part-LAT), and 39 did not receive LAT (non-LAT). More than 90% of patients presented ≤2 metastases. The T1/T2 stage (n=40, 78%) and N0/N1 stage (n=38, 74%) were mainly in the all site-LAT group. No patients with more than three metastases received LAT. Median PFS in the all site-LAT group improved, compared to the part-LAT and non-LAT groups (20.6, 15.6, and 13.9 months, respectively; P<0.001). Median OS in the all site-LAT, part-LAT, and non-LAT groups were 40.9, 34.1, and 30.8 months, respectively (P<0.001). The difference was statistically significant between patients in the all site-LAT group and the other groups, but it was not significant between the other two groups. In multivariate analysis, LAT of primary tumors was an indicator of good prognosis. Consolidative LAT for primary tumors, brain metastases, and adrenal metastases improved the median OS significantly (41). However, it is not clear if TKI was ultimately stopped in the all site-LAT group.

The randomized multicenter Phase 2 ATOM trial evaluated the feasibility of SRT at persistent active ¹⁸FDG-

PET sites after three months of EGFR-TKI (42). A maximum of four sites could be accessible to LAT. The study had to be stopped after three years, due to the low number of inclusions (16 patients included out of the 34 who were expected). A post-hoc analysis compared the 48 screen failure patients with the 16 included patients. The one-year PFS rate was 68.8%, and median OS was 43.3 months. No Grade ≥ 3 toxicity was observed. EGFR-TKI was stopped the day before SRT, and it was resumed the following day. The risk of progression in the LAT group was reduced, according to the post-hoc analysis (HR: 0.41; $P=0.0097$) (42).

Recently, the multicenter Phase 3 SINDAS trial was presented at the 2020 American Society of Clinical Oncology (ASCO) meeting, which evaluated the efficacy of up-front SRT to all disease sites, along with EGFR-TKI in EGFR-mutated OM-NSCLC patients (43). A maximum of five metastatic sites were allowed, whereas brain metastases were excluded. In the case of complete response, the duration of TKI treatment was not specified. The primary endpoint was PFS. Between 2016 and 2019, 133 patients were randomized: 65 (48.8%) in the TKI arm, and 68 (51.1%) in the SRT and TKI arm. Median PFS and OS significantly improved in the SRT group: 20.20 versus 12.5 months (HR: 0.68; $P<0.001$) and 25.50 versus 17.40 months (HR: 0.68; $P<0.001$), respectively, according to the interim analysis. In terms of tolerance, adverse events were similar, but more pneumonitis cases were noted in the SRT group (7.3% vs. 2.9%; $P>0.05$) (43).

In EGFR-mutated OM-NSCLC, the strategy of LAT of all tumor sites combined with TKI is feasible and appears to be associated with a good prognosis. These data need to be confirmed by randomized phase 3 trials.

LAT of all residual tumor sites could be performed in patients with lymph node involvement if controlled

Ni *et al.* specifically evaluated percutaneous microwave ablation (MWA) for the treatment of EGFR-mutated extracerebral OM-NSCLC, more than 50% of which presented lymph node mediastinal involvement (44). In this study, 86 patients with extracerebral OM disease and EGFR mutation were included, 34 of whom received locoregional treatment at the primary site (except for four) and metastatic sites after 2 months induction treatment with EGFR-TKI, whereas 52 patients were treated with EGFR-TKI alone. Patient characteristics were similar in the two groups, and most patients presented with less than three metastases ($n=75$, 87%) and advanced lymph node involvement (N2/N3; $n=49$, 57%). In the MWA group, the most common

metastatic sites were in the lung (39.5%) and liver (23.3%). Addition of MWA to EGFR-TKI significantly improved median PFS and OS, compared to the EGFR-TKI alone group: 12.9 versus 6.7 months (HR: 0.44; $P=0.02$) and 22.7 versus 4.8 months (HR: 0.45; $P=0.04$), respectively. Multivariate analysis reveals that consolidation MWA LAT is an independent predictor of better PFS and OS. MWA was well tolerated, and there were no Grade 3 toxicity. EGFR-TKI was continued during the intervention. MWA of the pulmonary lesions was complicated by pneumothorax in 18.6% of cases, which required chest tube aspiration in half of cases. The complications of MWA also included pain (mild or moderate in 58.8% of cases, and never severe) (44).

As previously described, it is our opinion that the only optimal strategy to cure OM patients with EGFR mutations is to curatively treat all the tumor sites, both primary and metastatic ones, with a combination of TKI. The availability of LAT techniques and questions concerning the duration of TKI treatment are limitations of this theory.

Which EGFR-TKIs and which timings are associated with LAT?

To date, most data concern EGFR-mutated OM-NSCLC patients that are treated with first- or second-generation EGFR-TKIs. Better control and better OS are obtained with osimertinib in metastatic EGFR lung cancer (6,45), but there is currently no available data on osimertinib to treat OM-NSCLC.

The timing of LAT introduction was not considered in the OM studies. A retrospective multicenter trial analyzed the optimal sequence of SRS or whole-brain radiation therapy (WBRT) and first- and second-generation EGFR-TKIs in patients with EGFR-mutated NSCLC who had brain metastases at diagnosis. Stereotactic radiosurgery followed by EGFR-TKI resulted in the longest OS, compared with upfront WBRT or EGFR-TKIs (46, 30, and 25 months, respectively; $P<0.001$) (46). However, osimertinib's better blood-brain barrier penetration and better activity against brain metastases could change this picture (47,48).

As previously explained, for OM-NSCLC with EGFR mutation, our proposal is to immediately initiate EGFR-TKIs, especially osimertinib in the case of brain metastases, and to then perform an assessment in order to ensure disease control before starting LAT. This reassessment must include ^{18}F FDG-PET and brain MRI to ensure disease control before starting LAT because about 1% and 7% of

patients with EGFR-mutated metastatic NSCLC present with initial progression (45).

Can we stop EGFR-TKIs after all-site lesions are treated with LAT, and if so, when?

If the treatment is aimed to obtain a cure, the question of stopping TKI should be raised for patients with completely all-site treated lesions. This question had not been studied in the literature. However, trials of adjuvant treatment in EGFR-mutated NSCLC may provide some answers. Currently, adjuvant EGFR-TKI improves disease-free survival (DFS), but an improvement in survival is not demonstrated yet in these studies (49-53).

The Phase 3 trial CTONG 1104 compared 24 months of gefitinib (n=111) with four cycles of a cisplatin–vinorelbine doublet (n=111) in adjuvant treatment of Chinese patients with completely resected Stage IIA–IIIA (N1–N2) EGFR-mutated NSCLC (52). The final OS results were presented at 2020 ASCO (51). At median follow-up of 80 months, adjuvant gefitinib administered for 24 months significantly improved DFS, but this advantage did not translate into a significant difference in OS. The updated median DFS was 30.8 months in the gefitinib group and 19.8 months in the CT group (HR: 0.56, 95% CI: 0.40–0.79). The median OS was 75.5 months in the gefitinib group and 62.8 months in the CT group (HR: 0.92, 95% CI: 0.62–1.36). Grade 3 or higher adverse events were less common with gefitinib (12% vs. 48%), and there were no cases of interstitial lung disease recorded.

This potentially better OS in completely resected N1/N2 patients with EGFR-mutated NSCLC was also evaluated in the EVAN study (53). This randomized, open-label Phase 2 trial compared erlotinib for 24 months with CT in adjuvant treatment of 102 completely resected Stage IIIA EGFR-mutated NSCLC patients. Median DFS was longer in the erlotinib group than in the CT group (42.4 vs. 21.0 months; HR: 0.268; P<0.0001). Although data were not mature, median OS had not been reached in either group at the data cut-off point, even if the HR for OS was 0.165 (95% CI: 0.047–0.579) in favor of erlotinib (P=0.0013), but.

Finally, in the ADAURA trial, a Phase 3 double-blind trial, 682 patients with EGFR-mutated Stage IB to IIIA resected NSCLC were randomized to adjuvant osimertinib administered for up to three years, versus placebo. Adjuvant CT was authorized in both groups. The early results of this trial were presented at 2020 ASCO (54,55). The Data Safety Monitoring Committee recommended ending the

study early, due to an improvement of two-year DFS in the osimertinib group (89% vs. 53%; HR: 0.21). OS data were not yet mature. The recurrence of central nervous system-related disease was reduced by 82% with osimertinib. Osimertinib was well tolerated, with serious adverse events observed in 16% of cases, versus 13% in the placebo group.

To date, we do not have any evidence that TKI in an adjuvant setting of completely resected EGFR-mutated NSCLC receiving or not CT improves OS, although it reduces or delay the risk of metastatic relapse, rather than locoregional relapse. Therefore, in OM disease, it is difficult to administer the EGFR-TKI for less than two or three years, and this is probably only applicable to patients with good prognosis factors, which are yet to be identified. Actually, the place of adjuvant CT should not be challenged.

Therapeutic strategies for oligo-progressive oncogenic-driven NSCLC

Unlike the management of synchronous OM, many recommendations describe the management of oligo-progression in oncogenic-driven advanced NSCLC (2,56). At oligo-progression, the aim is not to cure patients, but to postpone changing the therapeutic line.

The first retrospective single institution study that demonstrated the benefit of LAT in oligo-progression in oncogenic-driven NSCLC was published in 2012 (57). Weickhardt *et al.* described the natural history of 38 ALK-fusion NSCLC and 27 EGFR mutated-driven NSCLC patients, after they had progressed within the central nervous system (but were not non-leptomeningeal). Patients had <4 systemic sites under TKI (erlotinib or crizotinib) (58). LAT (all but one using RT) was performed in 25 patients with oligo-progression (49%; 15 ALK fusion-driven and 10 EGFR mutated-driven) with initial TKI continuation. Finally, 19 of 25 patients progressed after LAT administration in a median time of 6.2 months (3.7–8.0 months). LAT was well tolerated, with two cases of grade 3 adverse events after WBRT (both fatigue).

In a retrospective study of oligo-progressive EGFR NSCLC, 46 patients were treated with LAT (all with RT except two with radiofrequency ablation of the lung), and the same TKI was continued (59). Twenty-four (52.2%) patients were treated for brain metastases (there was no limit on the number of brain metastases), 16 patients (34.8%) were treated for lung metastases, and six patients (13%) were treated for bone metastases. Median PFS and OS after LAT were 7.0 and 13.0 months, respectively.

Two-year OS was 65.2%. Del19 EGFR mutations, brain metastases sites of LAT (*vs.* lung or bone), and a long period since the first progression to LAT were all good prognostic factors for OS after LAT. Grade 3 pneumonitis was observed in two patients (4.3%).

In another retrospective cohort, Rossi *et al.* reported 131 patients with disease progression during first-line afatinib or gefitinib (60). LAT with high-dose RT and TKI continuation were conducted on 30 patients. The sites of local RT were the bone (n=11), lung (n=9), brain (n=8), lymph nodes (n=8), and liver (n=1). Median OS was longer in the LAT patient group than for patients continuing TKI beyond progression without LAT or those switching to another systemic therapy (37.3, 20.1, and 15.1 months, respectively; $P < 0.0001$).

Finally, a Phase 2 trial evaluated SRT for the treatment of patients with oligo-progression on erlotinib (61). Twenty-five out of the 40 patients who progressed with less than five sites, including brain metastases, were ultimately treated. For most patients (84%), one metastatic site was treated. The treated metastases were on the lung (n=15), bone (n=7), liver (n=4), and brain (n=2). Median PFS from SRT was six months. No toxicity Grade 3/4 was attributed to SRT. The study closed early due to poor accrual and because of the development of osimertinib. This study demonstrated the feasibility of SRT followed by the re-initiation of TKI for patients with oligo-progression.

Can we safely combine LAT and kinase inhibitors?

Safety data on the undesirable effects of percutaneous ablation in association with targeted therapies needs further confirmation, due to the limited amount of evidence in the literature (44,62). Most percutaneous radiofrequency, microwave ablation, and cryoablation procedures were well tolerated in the lungs (57), and the rate of major complications was inferior to 10%. Pain was the most common complication, mostly of mild intensity and observed in one-third of patients. Postoperative pneumothorax was recorded in up to 30% of procedures, with chest tube drainage only rarely required. No patients have died during or within 30 days after these procedures.

Most available data concern RT. A dose-fractionation RT regimen with curative intent was dependent on the radiation oncologist team, accelerators, experience, and the patient's metastasis (size, motion, location). For example, in a combined LAT and TKI retrospective study, the accepted definition of RT included standard-fractionation RT

(60 Gy in 2-Gy fractions), aggressive palliation RT (45 Gy in 3-Gy fractions), SRS, and SABR (from 20 to 40 Gy in 1–5 fractions) (41).

In lung SBRT for early-stage NSCLC, biological equivalent doses of >100 Gy have been associated with high local control (63). In a phase 3 randomized trial that included 101 patients, the efficacy of SABR was shown to be superior to conventional RT for localized NSCLC, without excess toxicity (64). For brain metastases, data suggest that the prescription is the main factor associated with local control after SRS (65). Additionally, for bone-metastasis RT, SBRT was associated with higher pain relief and local control versus conventional palliative RT in a phase 2 trial that included 160 patients (66). This is similar to SBRT for liver metastasis, where conventional RT is scarcely used. However, SBRT is associated with high local control rates (67). These data favor RT that uses stereotactic techniques and delivers ablative doses.

Studies of tolerance with combined targeted therapies and SRT are retrospective and heterogeneous. The best available safety data for SRS and SABT combined with small molecules or antibodies are those with bevacizumab, ipilimumab, nivolumab, and EGFR-TKIs (68). The heterogeneity of RT concerns the techniques used, doses delivered, target organs, and volumes of the treated lesions. The majority of recommendations propose a break in TKI treatment before and after RT or a sequential treatment that starts with SRT for the treatment of brain metastases.

EGFR-TKIs that are associated with extracranial SABR may be associated, yet with increased toxicity in the irradiated volume when treating abdominal and thoracic metastases. Nevertheless, no increased toxicity was observed in the cranial SRS (68).

Regarding ALK inhibitors that are associated with SABR and SRS, only few safety data are available. An Italian RT group conducted a retrospective multicenter study to evaluate the impact of RT among 106 NSCLC patients that had been treated with RT concomitantly to EGFR- and ALK-TKIs (30 days before or after) between 2010 and 2016. RT was either palliative or stereotactic. SRT was administered to 49 patients (46%). The RT site was in the brain (46%), bone (27%), and lung (14%). No TKI was stopped for toxicity, and the TKI was continued in most patients (38/62, 63%) (39). In multivariate analysis, SRT was associated with improved survival (39).

With regards to BRAF inhibitors, high rates of brain toxicities (mainly hemorrhagic complications) have been described after cerebral SRS in metastatic melanoma

patients, which suggests that caution is required. There are no data on the combination of BRAF inhibitors with extracerebral SABR (68,69), and the limited number of patients treated with MEK inhibitors and SRS or SABR inhibitors do not allow for conclusions to be drawn about the safety of such combinations. In 2016, the Eastern Cooperative Oncology Group (ECOG) recommended administering both BRAF and MEK inhibitors ≥ 3 days before and after fractionated RT and ≥ 1 day before and after single-dose SRS (70).

In HER2-positive breast cancer patients, lapatinib concurrently with brain SRS did not increase radiation necrosis rates after a 12-month follow-up (71). On the other hand, another retrospective study revealed that TDM1 with brain SRS was associated with higher radiation necrosis risk (72). In another study, sequential SRS treatment lowered radiation necrosis, versus concurrent TDM1 use (29% vs. 50%) (73).

Finally, there are only preliminary published data concerning the combination of curative intent RT and TKIs. The precautionary principle would be to take a TKI break at a maximum of five treatment half-lives before, especially when potential TKI and RT interaction toxicity can occur in the organ concerned by the RT field (brain, lung) (74). In this context, curative intent RT should prioritize stereotactic techniques and ablative doses in order to optimize local control, reduce irradiated volumes, and shorten or maybe avoid the TKI break.

Conclusions

Nowadays, with innovative strategies that include targeted therapies and LAT combinations, synchronous OM with oncogenic-driven NSCLC might represent an opportunity for an attempt-to-cure multimodal therapeutic approach to be developed. No studies have specifically examined the management of OM patients with addictions (i.e., ALK, ROS, or BRAF) other than EGFR-driven NSCLC. This is probably due to the rarity of the OM presentation and of each of the different known oncogenic addictions. Similarly, almost all published data relates to Asian populations and should be interpreted with caution for Caucasian populations.

In attempt-to-cure OM EGFR-mutated NSCLC, the optimal strategy might be to introduce an EGFR-TKI, then treat all tumor sites with LAT, and finally continue TKI for at least two or three years. At the very least, this strategy will prolong PFS, improve OS for some patients, and potentially lead to a cancer cure for a few patients.

Some clinical factors pattern of OM disease (brain and lung), therapeutic aspects (ability to treat all the tumor sites, strength of efficacy of the targeted therapy) and molecular factors (initial molecular tumor heterogeneity and ability to rapidly clear the residual tumor) can help select the best candidate for an attempt-to-cure approach.

Circulating tumor DNA (ctDNA) may be a biomarker for minimal residual disease and can reliably identify patients at high risk for recurrence. Assessments of EGFR mutational status in the ctDNA of patients with NSCLC have demonstrated high specificity but limited sensitivity (75). ctDNA can identify recurrence significantly earlier than routine CT imaging. Development of a highly sensitive next-generation sequencing (NGS) technique is required to detect low-concentration mutations in ctDNA. For example, personalized cancer profiling using deep sequencing (CAPP-seq), an NGS-based method that tracks multiple mutations per patient, can achieve lower limits of detection $\sim 0.002\%$. Postoperative detection of ctDNA has a very high risk of future relapse (HR: 43.4, 95% CI: 5.7–341), with a median 5.2-month lead time over clinical progression (76,77). In the future, new strategies should integrate liquid biopsy into treatment of OM with oncogenic-driven NSCLC.

Finally, the types of consolidative LAT must be determined in multidisciplinary team meetings, depending on the technique availability at that site. Prospective, multi-institutional, randomized trials of LAT combinations with a last-generation TKI are needed to establish better OM oncogenic-driven NSCLC strategies.

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